

REMARKS

This Amendment is in response to the Examiner's Official Action mailed January 19, 2005. Claims 5-8, 10-13, 18-25 and 28-30 are cancelled. Claims 1-4, 9, 14-17 and 26-27 are amended. Claims 1-4, 9, 14-17 and 26-27 are now pending.

Reconsideration of the application is respectfully requested in view of the above amendments to the claims and the following remarks. For the Examiner's convenience and reference, Applicants' remarks are presented in the order in which the corresponding issues were raised in the Office Action.

I. Rejection under 35 U.S.C. §112, Second Paragraph

Claims 10-13 stand rejected under 35 U.S.C. §112, Second Paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the inventions. Specifically, the Examiner stated that the claim is a dependent claim that reference to itself. Applicants' cancellation of claims 10-13 renders the rejection moot.

II. Rejection under 35 U.S.C. §102(a)

Claims 1-8 and 10-20 stand rejected under 35 U.S.C. §102(a) as being anticipated over the disclosure of Wall et al. (US Patent No. 6,288,072). Applicants respectfully traverse the Examiner's rejection based on the following reasons.

Independent claim 1 as amended is directed toward a crystal form of 9-nitrocamptothecin which is crystal form C as described in the Specification on pages 16-17. 9-nitrocamptothecin crystal form C has the following specific spectral characteristics: i) by differential scanning calorimetry, no observable endotherm and an exotherm at between 273.6 and 275.6°C; and ii) a solution NMR spectrum with multiplets at 1.7 and 3.7 ppm shifts; and iii) an X-ray powder diffraction pattern with diffraction lines at 2θ values 6.7, 12.5, 14.0 and 23.9 for Cu $K\alpha$ radiation of wavelength 1.5406 Angstrom. Independent claim 14 specifies a pharmaceutical composition comprising crystal form C of 9-nitrocamptothecin.

For a rejection of claims under 35 U.S.C. § 102 to be properly founded, the Examiner must establish that a single prior art reference either expressly or inherently discloses each and every element of the claimed invention. *See, e.g., Verdegaal Bros. v. Union Oil Co. Of California*, 2

814 F.2d 628, 631, USPQ 2d 1051, 1053 (Fed. Cir. 1987). In *Scripps Clinic & Research Found v. Genentech, Inc.*, 927 F.2d 1565, 18 USPQ 2d 1001 (Fed. Cir. 1991), the Federal Circuit held that in view of the person of ordinary skill in the art, there must be no difference between the claimed invention and the disclosure in the cited reference. Anticipation can be found, therefore, only when a cited reference discloses all of the elements, features or limitations of the presently claimed invention.

First, the cited reference, Wall et al., fails to disclose the specific compound recited in the pending claims, 9-nitrocamptothecin. Instead, Wall et al. discloses 9-nitro-10,11-methylenedioxy-20-O- β -ala-lys-20-(S)-camptothecin (column 5, lines 49-50) and 9-nitro-20-O- β -ala-20-(S)-camptothecin (column 6, line 15). These compounds are completely different from 9-nitrocamptothecin in chemical structure.

Second, Wall et al. fails to disclose a crystal form of 9-nitrocamptothecin having the specific spectral characteristics specified in claim 1. Although this reference describes in general camptothecin compounds, their solvates, hydrates, polymorphs, salts, etc., as acknowledged by the Examiner, it is silent as to the particular properties recited in claim 1.

However, in an effort to bridge the gap between the disclosure in Wall et al. and the claimed invention, the Examiner relied on an inherency theory that the limitations recited in claim 1 would be inherent to any 9-nitrocamptothecin compound. Pursuant to MPEP 2112,

"To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted) ... "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original)

The Examiner has not met the burden of providing a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent spectral characteristics specified in claim 1 necessarily flow from the teachings of Wall et al. As discussed above, Wall et al. does not disclose 9-nitrocamptothecin, let alone teaching a specific crystal form of 9-nitrocamptothecin

having the spectral characteristics.

Since Wall et al. fails to teach all of the elements, features or limitations of the presently claimed invention, it fails to anticipate the claimed invention under 35 U.S.C. §102(a). Withdrawal of the ground of rejection is therefore respectfully requested.

II. Rejection of Claims 1-8 and 14-20 under 35 U.S.C. §103(a)

Claims 1-8 and 14-20 stand rejected under 35 U.S.C. §102(a) as being anticipated, or in the alternative, under 35 U.S.C. §103(a) as being obvious over the disclosure of Wall et al. (US Patent No. 6,288,072). Applicants respectfully traverse the Examiner's rejection based on the following reasons.

To establish a prima facie case of obviousness, the Examiner bears the burden of proving 1) the prior art reference (or references when combined) must teach or suggest all the claim limitations; 2) the prior art contains a suggestion or motivation to combine the prior art references in such a way as to achieve the claimed invention; and 3) one of ordinary skill in the art at the time the invention was made would have reasonable expectation of success of the claimed invention. *In re Vaeck*, 947 F. 2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); *In re O'Farrell*, 853 F. 2d 894, 903-904, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988); and *In re Dow Chem.*, 837 F. 2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

As discussed above, Wall et al. neither teaches 9-nitrocamptothecin nor describes the particular spectral characteristics of 9-nitrocamptothecin in crystal form C. And the Examiner has not met the burden of providing a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent spectral characteristics specified in claim 1 necessarily flow from the teachings of Wall et al. Absent such a fact or technical reasoning, the Examiner's imposition of the burden on Applicant to prove that the claims products are functionally different than those taught by Wall et al. is improper.

As the cited reference fails to teach every elements of independent claims 1 and 14, a prima facie case of obviousness has not been established under 35 U.S.C. §103(a). Withdrawal of the ground of rejection is therefore respectfully requested.

III. Rejection of Claims 9 and 21-30 under 35 U.S.C. §103(a)

Claims 9 and 21-30 stand rejected under 35 U.S.C. §103(a) as being unpatentable over the combined disclosure of Wall et al. (US Patent No. 6,288,072) and Comins et al. (US Patent No. 5,162,532). Applicants respectfully traverse the Examiner's rejection based on the following reasons.

Claim 9 as amended is dependent from independent claim 1. Claim 21- 25 have been canceled. Claim 26 is directed to a method of preparing crystal form C of 9-nitrocamptothecin as specified in claim 1.

As discussed above, Wall et al. neither teaches 9-nitrocamptothecin nor describes the particular spectral characteristics of 9-nitrocamptothecin in crystal form C. On the other hand, Comins merely discloses using solvent such as tetrahydrofuran in the synthesis of pyridone intermediates of formula III (column 3, lines 45-49). In fact, in the synthesis of the final product, (+)-camptothecin (which is a different compound from 9-nitrocamptothecin), the yellow solid of the product was purified by using silica gel and 4% CH₃OH/CHCl₃. Thus, Comins also fails to teach using tetrahydrofuran to prepare crystal form of 9-nitrocamptothecin.

In view of failure of the cited references, each alone or in combination, to teach every elements of independent claims 9 and claim 26, a prima facie case of obviousness has not been established under 35 U.S.C. §103(a). Withdrawal of the ground of rejection is therefore respectfully requested.

CONCLUSION

In view of the above amendment and remarks, Applicants earnestly believe that they are entitled to a letters patent, and respectfully solicit the Examiner to expedite prosecution of this patent application to issuance. Should the Examiner have any questions, Examiner is encouraged to telephone the undersigned.

Respectfully submitted,

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